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Research Article

MOLECULAR DOCKING STUDIES & DRUG DESIGN OF NEWER IMIDAZOLE DERIVATIVES AS CLK1 INHIBITOR

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ABSTRACT

Molecular docking has been used as a tool for modern drug design as well as for understanding drug receptor interactions. In the present study imidazole derivatives were designed and screened for molecular docking (using Schrodinger, ligand minimization by Ligprep, docking by GLIDE XP protocol) against Cdc2-Like Kinase 1 (CLK1) as drug-gable target. Among all designed derivatives, 4 derivatives (P1, P2, P3 and P5) have minimum binding energy and also had high affinity towards pocket of CLK1 kinase. Out of these P2 was most active (energy -9.642 kcal/mol) and showed highest affinity towards CLK1 kinase. With these results, we can conclude that these derivatives might be having anti-cancerous, as well as antibacterial activity.

Keywords: Docking, Drug-gable, CLK1 kinase, Anticancer, Antibacterial

1. INTRODUCTION

In the current study attempt has been made to evaluate that inhibition of Cdc2 like kinase (CLK1) efficiently induced autophagy [1]. CLK1 were targeted for autotophagy related diseases, few of them are selective and others are miscellaneous type [2, 3] and thus are unsuitable due to their side effects [4] (Fig. 1). CLK1 inhibitors should be potent and selective to cure autophagy related diseases like cancer, diabetes [5, 6] neurogenerative diseases [7- 9] and organ injury [10, 11]. In authophagy there is removal of damaged and useless organelles and proteins to protect cell death [12], impaired activity may cause many diseases in autophagy, there may be a disturbance in the immune system [13], it may cause insulin resistance in the human body [14, 15].

2. Material and Methods [12]

2.1. Molecular docking studies

Docking study was performed by using Schrodinger with GLIDE XP protocol, high docking accuracy and enrichment was achieved by the help of GLIDE XP across a diverse range of receptors.

2.2. Ligand preparation and minimization:

Ligand preparation was done by Ligprep [16]. For the identification of lead compound it is necessary to have 3D structure. Ligprep converts the 2D structure to 3D structure. This conversion is a key precursor for computational analysis. It is also helpful in eliminating the mistakes in ligand to reduce computational error.

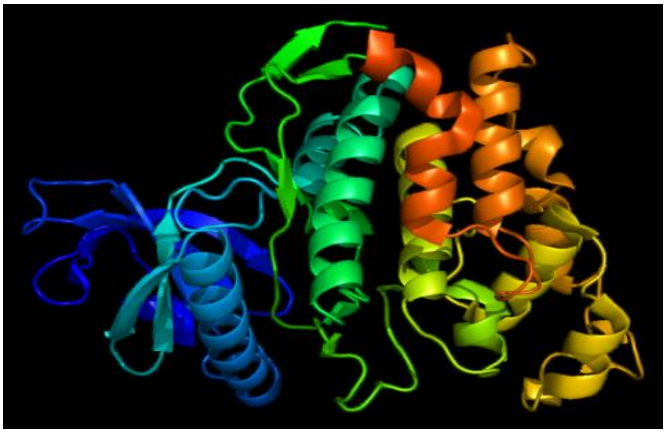


Fig.1: Ribbon like Structure of CLK1

2.3. Protein preparation and minimization

Protein preparation and minimization was done by using protein preparation wizard (PDB 5X8l), it automatically import PDB files from local database or PDB website (protein data bank).

2.4. Active site identification

After the completion of the model, the binding sites of CLK1 were searched, based on the structural comparison

of the template (Fig. 2). The hydrogen present on the imidazole nitrogen and methyl group formed a hydrogen bond with kinase LEU 24 and ASP 250.

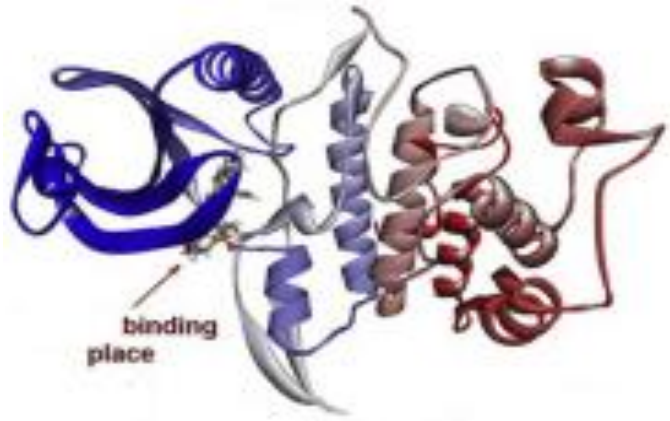


Fig.2: Active Site identification of drug

2.5. Grid formation

Auto dock needs a pre-calculate grid map, for each atom type present in ligand to be docked. This makes docking calculation very fast and easy. Autogrid is used to calculate these maps. These maps consist of a three dimensional lattice of spaced points, centered and surrounded (Fig. 3) on same region of interest of macromolecule under study. It could be a protein, antibody, enzyme, DNA, RNA or even ionic crystals. The grid point spacing taken in this process is 1.9Å.

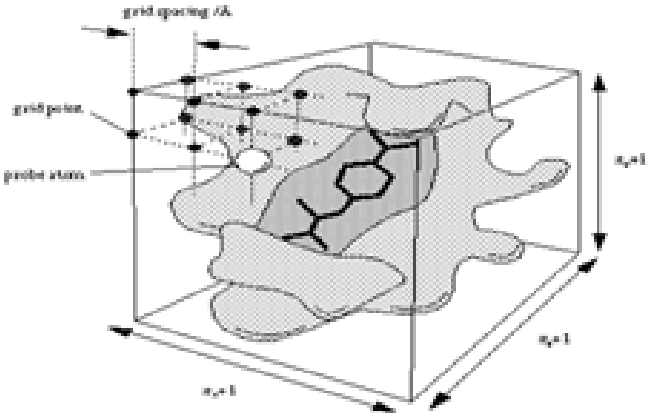
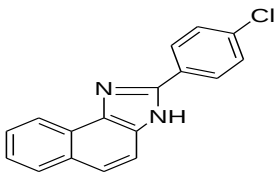
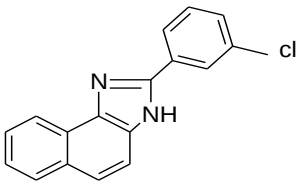
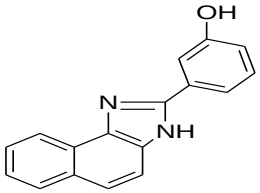


Fig. 3: Illustration of the main features of a grid map in molecular docking

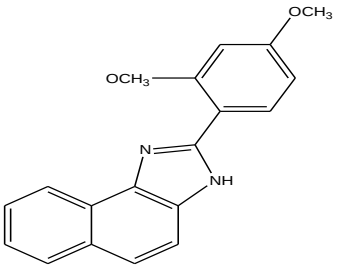
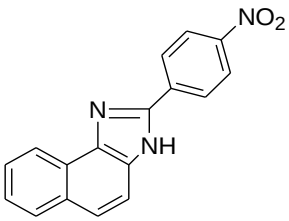
3. RESULTS AND DISCUSSION

Molecular docking studies for 11 compounds which are involve in anticancer mechanisms has been performed and the docking score based on hydrogen bonded residue and hydrophobic interaction such as alkyl group were provided. The compound P1, P2, P3, P5 showed a docking score -9.381 kcal/mol, -9.642 kcal/mol, -8.486 kcal/mol, -8.021 kcal/mol, out of them ligand P2 showed better binding score with CLK1 protein and formed hydrogen bond with LEU 244, P3 formed the hydrogen bond with LEU 244, P3and P5 showed bond formation with protein LEU 244 and ASP 250 (Table1).

Table 1: The Binding affinity/dock score (ΔG) (kcal/mol) of the ligand with an targeted protein and their comparative studies

S. No.	Structure of compounds	Dock score of the ligand		
		Ligand name	Energy	Activity against CLK1
1.		LIGAND 1 (P1)	-9.381 kcal/mol	----
2.		LIGAND 2 (P2)	-9.642 kcal/mol	Most active
3.		LIGAND 3 (P3)	-8.486 kcal/mol	----

Continued….

4.		LIGAND 4 (P4)	7.403 kcal/mol	Least active
5.		LIGAND 5 (P5)	-8.021 kcal/mol	----

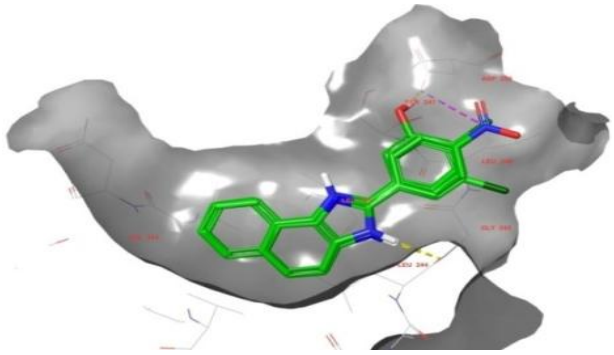


Fig. 4: Over lapped view of all the ligands

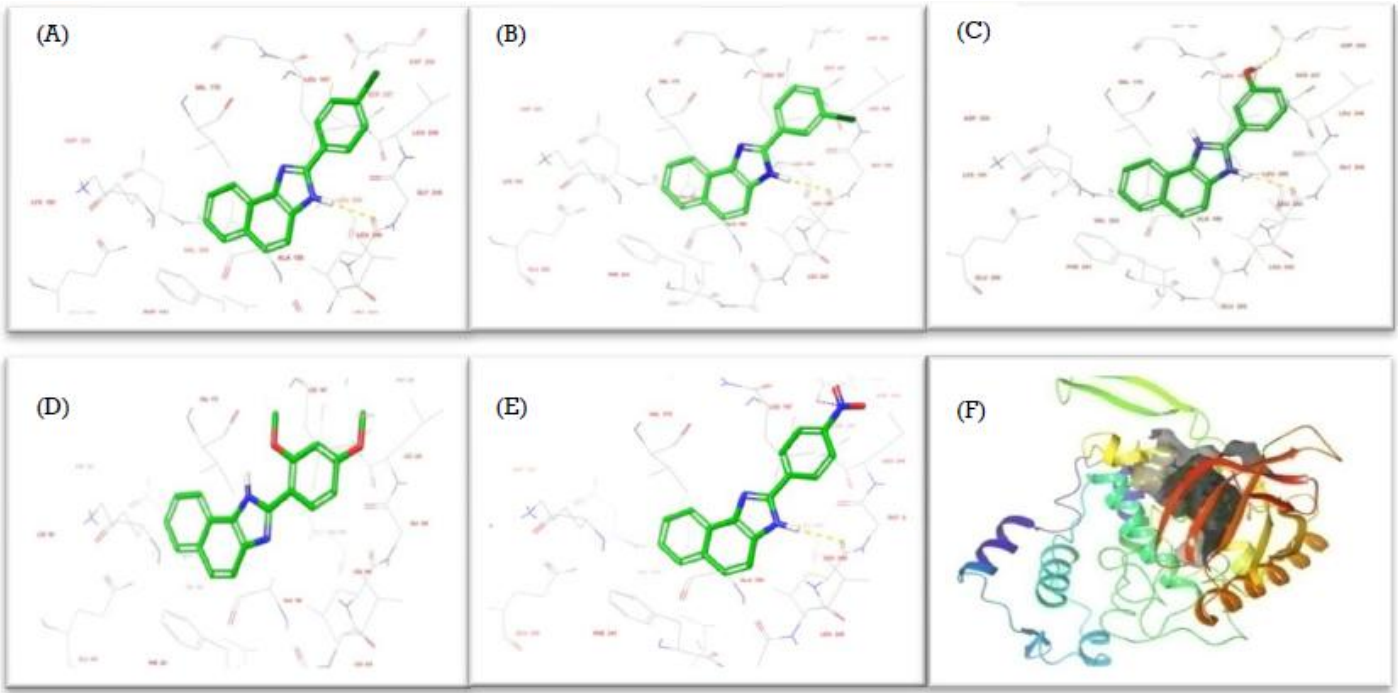


Fig. 5: Images showing the binding interaction of compounds with some proteins of CLK1
(A) Binding interaction of P1 with CLK1 protein. (B) Binding interaction of P2 with CLK1 protein. (C) Binding interaction of P3 with CLK 1 protein. (D) Binding interaction of P4 with CLK1 protein. (E) Binding interaction of P5 with CLK1 protein. (F) Ribbon like structure of a drug receptor attachment.

In the overlapped view, all the ligands are superimposed on each other to measure the binding affinity with the receptor and protein as shown in fig. 4, all the ligands are first superimposed individually and then docked to get docking score (Fig. 5 A, B, C, D, E). The overlapped ligands are then bind with the enzyme and then it will form a ribbon like structure. (Fig. 5F).

4. CONCLUSION

After the docking study it is concluded that ligand P2 showed good binding affinity to target protein of CLK1 with the existence of hydrogen bonding. The result showed the possibility of presence of anti-cancerous and antibacterial activity in the ligand. Ligand P2 can serve as a lead compound for structural modification to design a new anti-cancerous and antibacterial study.

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Conflict of Interest

The authors declare to have no conflict of Interest.

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